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Predictors of catheter-related gram-negative bacilli bacteraemia among cancer patients

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Abstract

Gram-negative bacillary bacteraemia (GNB) is associated with high morbidity and mortality among cancer patients. We conducted this study to determine the risk factors that may predict the catheter as the source of GNB in cancer patients. From July 2005 to December 2006 all 266 cancer patients with GNB and central venous catheters (CVCs) at The University of Texas M. D. Anderson Cancer Centre in Houston, were classified as catheter-related bloodstream infection (CRBSI) according to Infectious Diseases Society of America criteria. We compared clinical and microbiological features of CRBSIs and non-CRBSIs. We identified 78 CRBSIs and 126 non-CRBSIs. On univariate analysis, polymicrobial bacteraemia, *Stenotrophomonas maltophilia* bacteraemia, and more than 1000 CFUs in CVC blood cultures, were more common among CRBSI cases. *Escherichia coli* bacteraemia, haematologic cancer, neutropenia and prior antibiotic use were more common among non-CRBSI cases. On multivariate analysis, *S. maltophilia* bacteraemia (odds ratio (OR), 5.78; 95% confidence interval (CI), 1.47–22.78; p 0.045), polymicrobial bacteraemia (OR, 4.04; 95% CI, 1.56–10.44; p 0.042), and more than 1000 CFUs from CVC blood cultures (OR, 4.39; 95% CI, 2.02–9.27; p <0.01), were associated with CRBSI. Neutropenia was associated with non-CRBSI (OR, 0.26; 95% CI, 0.13–0.53; p <0.01). Several factors such as *S. maltophilia* bacteraemia, polymicrobial bacteraemia and more than 1000 CFUs from a blood culture drawn through the CVC may assist the clinicians in assessing whether an indwelling catheter is the source of a GNB and hence CVC removal may be considered.

Keywords: Bacteraemia, catheter-related infection, gram-negative bacilli, neutropenia, *Stenotrophomonas maltophilia*
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Introduction

Gram-negative bacilli cause a sizeable proportion of nosocomial bloodstream infections in the US. Recent multiannual and multicentre reports have shown that gram-negative bacilli cause a similar proportion of nosocomial bacteraemias in different settings, such as general admissions (25%) [1] and critical care unit admissions (24%) [2], and among cancer patients (27%) [3]. At our institution, Raad *et al.* [4] also found that one-quarter of bloodstream infections among cancer patients were caused by a gram-negative organism, and more than half of bacteraemias were catheter related. Gram-negative bacteraemias (GNB) have mortality rates of up to 38%, according to recent reports [5–7]. Patients with cancer and bacteraemia have higher 30-day mortality than patients without malignancy [8].

Despite its frequency, there are only a limited number of studies describing the microbiological and clinical characteristics of gram-negative catheter-related bloodstream infections (CRBSIs). Hanna *et al.* [9] reported that early central venous catheter (CVC) removal is critical in preventing relapse of gram-negative CRBSI among cancer patients. However, in many patients with CVCs and GNB, the source of infection is not related to catheters and removal of the indwelling device is unnecessary and might deprive severely ill patients of a needed vascular access. In this current study we aimed to determine predictors of CRBSI among cancer patients with CVC and GNB. These clinical and microbiological predictors

will serve as helpful criteria that will guide clinicians at the bedside as to whether the CVC is to be removed or retained.

Patients and Methods

Clinical characteristics

We performed a retrospective study on cancer patients with GNB and a CVC in place from July 2005 to December 2006 at The University of Texas M. D. Anderson Cancer Centre, an oncological hospital with 500 beds in Houston, Texas. The Institutional Review Board approved this study and waiver of informed consent was obtained.

Blood cultures were processed using the BACTEC 9240 automated culturing system (Plus Aerobic/F bottles; BD Diagnostic Systems, Sparks, MD, USA) and the Isolator 10 system (Wampole Laboratories, Cranbury, NJ, USA). We routinely performed paired quantitative blood cultures. The number of colony-forming units had been quantified from 10 mL of blood cultured on plates. Time to positivity was recorded for blood cultures taken from the CVC and peripherally.

We compared patients with CRBSIs with those with non-CRBSIs in terms of: sex; signs of infection, such as fever, chills, hypotension, and local inflammation at the CVC site; clinical characteristics, such as neutropenia (defined as an absolute neutrophil count <500), cancer type (haematological or non-haematological), admission to the critical care unit, surgery during the month prior to positive blood culture, total parenteral nutrition, mucositis, stem cell transplantation, duration of CVC use, CVC location and number of lumens, and prior antibiotic use; and the microbiological features of the bacteria, including species, number of colonies, if the blood culture was polymicrobial (defined as more than one isolate from a single blood culture) and proportion of multidrug-resistant isolates (defined as resistant to a quinolone, an aminoglycoside, and an extended-spectrum cephalosporin).

We assessed concordance by contrasting the predictive probability calculated for each subject grouped into pairs (one with CRBSI and one with non-CRBSI) with the actual findings. When the predicted probability of CRBSI of the subject with CRBSI is higher than the probability of the subject with non-CRBSI we say that the pair is concordant. Conversely, if the predicted probability of CRBSI is lower for the subject who did have infection then we say that the pair is discordant. When the predicted probability is the same, the pair is tied.

Definitions

Bloodstream infection (BSI) was defined as a recognized pathogen, isolated from blood culture, that is not related to infection at another site in a patient who had fever (>38°C), chills or rigors, or hypotension.

Antibiotic exposure was defined as a patient who received any antibiotic more than 24 h prior to the time when the positive blood cultures were drawn.

Catheter-related bloodstream infection (CRBSI) was defined as a BSI plus one of three conditions: first, the isolation of the same organism from quantitative culture of the catheter tip (>100 CFU/mL) and blood; second, a >3:1 ratio of simultaneous quantitative blood cultures drawn from a CVC compared with peripheral blood culture; or third, differential time to positivity of more than 2 h (blood culture drawn from the catheter becomes positive at least 2 h earlier than a simultaneously drawn peripheral blood culture) [10].

Statistical analysis

We compared categorical variables using the chi-square test and Fisher's exact test when appropriate. We determined whether our recorded continuous variables followed a normal distribution using the Shapiro–Wilk test. We used the Wilcoxon test to compare the distribution of these variables between CRBSI and non-CRBSI cases. We included all variables whose tests for association with CRBSI rendered a p-value of ≤0.25 in a multiple logistic regression model and tested in a descending way. All tests were two tailed, with a level of significance of 0.05. We used SAS software version 9 (SAS Institute, Cary, NC, USA) for all statistical analyses.

Results

From July 2005 to December 2006, there were 623 episodes of bacteraemia (Fig. 1) among cancer patients with CVCs. In 266 cases (42.7%), at least one isolate was identified as gram-negative bacilli. Seventy-eight cases of GNB were classified as definite CRBSI, whereas 126 were classified as non-CRBSIs. Another 62 cases were classified probable CRBSI and excluded from the analysis.

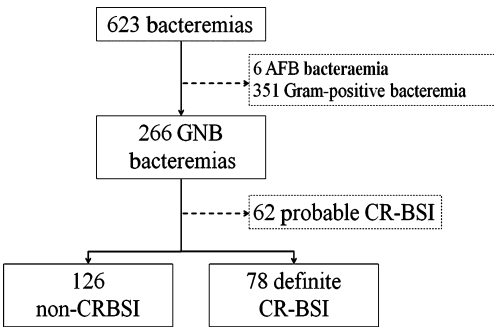

FIG. 1. Flow chart showing selection of patients.

Univariate analysis

The age distribution was similar between patients with CRBSIs and those with non-CRBSIs (median age, 59 years for CRBSI patients vs. 56 years for non-CRBSI patients, p 0.68). Both groups had a similar sex distribution (50% male for CRBSIs vs. 56% for non-CRBSIs; p 0.44). The median duration of CVC use was also similar (58.5 days for CRBSIs vs. 42.0 days for non-CRBSIs; p 0.12). There was a similar proportion of patients with a CVC in place for at least 50 days in both groups (53% of those with CRBSIs vs. 44% of those with non-CRBSIs; p 0.18).

There were statistically significant differences in the microbiological characteristics of CRBSIs and non-CRBSIs (Fig. 2). *Escherichia coli* was found more frequently in non-CRBSI cases than in CRBSI cases (33% vs. 15%; p 0.005). Conversely, *Stenotrophomonas maltophilia* was more common in CRBSIs (3% non-CRBSIs vs.14% CRBSIs; p 0.004). Two-thirds (36 of 54) of CVC blood cultures with a colony count of >1000 CFUs were from patients with CRBSIs (p <0.0001). Only 15 of 204 GNB isolates were multidrug resistant (resistance to an aminoglycoside, a cephalosporin and a quinolone). These isolates found were equally apportioned between CRBSI and non-CRBSI patients (4% and 10%, respectively; p 0.13).

Systemic and local signs of infection were similarly distributed in both groups (Table 1). Patients with CRBSI were less likely to have a haematological malignancy than those with a non-CRRBSI (64% vs. 81%; p 0.007). One hundred and eighteen patients had neutropenia; 100 of these patients (93%) had haematological malignancies. Neutropenia was also strongly associated with non-CRBSIs (36% among CRBSIs vs. 71% among non-CRBSIs; p <0.0001). Patients with CRBSIs and non-CRBSIs had similar distributions of other presumptive risk factors for bacteraemia, including stem cell transplantation (13% in patients with CRBSIs vs. 10% in patients with non-CRBSIs; p 0.58), admission to the critical care unit (9% vs. 11%; p 0.63), prior surgery (3% vs. 6%; p 0.49), total parenteral nutrition (3% vs. 1%; p 0.56), mucositis (6% vs. 8%; p 0.61), and graft-versus-host disease (4% vs. 0%; p 0.06). Thirty-eight of 78 patients with CRBSIs had previously used antibiotics vs. 86 of 126 with non-CRBSIs (p 0.006). Three of four antibiotic prescriptions were given as prophylaxis.

TABLE 1. Relationships between clinical variables and gram-negative CRBSI

Variable	CRBSI (*n* = 78)	Non-CRBSI (*n* = 126)	p-value
Male sex, *n* (%)	39 (50)	70 (56)	0.44
Median age, years	59	56	0.68
Fever, *n* (%)	64 (82)	100 (79)	0.64
Chills, *n* (%)	17 (22)	17 (14)	0.12
Hypotension, *n* (%)	13 (17)	19 (15)	0.76
Local tenderness, *n* (%)	0 (0)	5 (4)	0.16
Neutropenia, *n* (%)	28 (36)	90 (71)	<0.0001
Haematological malignancy, *n* (%)	50 (64)	102 (81)	0.0073
Critical care unit admission, *n* (%)	7 (9)	14 (11)	0.63
Previous surgery, *n* (%)	2 (3)	7 (6)	0.49
Total parenteral nutrition, *n* (%)	2 (3)	1 (1)	0.56
Mucositis, *n* (%)	5 (6)	10 (8)	0.61
Stem cell transplantation, *n* (%)	10 (13)	13 (10)	0.58
Graft-versus-host disease, *n* (%)	3 (4)	0 (0)	0.06
Median duration of catheterization, days	58.5	42	0.12
CVC in place ≥50 days, *n* (%)	41 (53)	56 (44)	0.18
Multiple-lumen CVC, *n* (%)	65 (83)	98 (78)	0.34
Catheter location			0.67
Subclavian	56 (76)	83 (67)	
Jugular	3 (4)	4 (3)	
Femoral	0 (0)	1 (1)	
Cephalic	2 (3)	5 (4)	
Basilic	13 (18)	30 (24)	
Antibiotics exposure, *n* (%)	38 (49)	86 (68)	0.0055
BSI organism, *n* (%)			
S. maltophilia	11 (14)	4 (3)	0.0037
E. coli	12 (15)	42 (33)	0.0047
Acinetobacter spp.	8 (10)	4 (3)	0.06
E. cloacae	10 (13)	8 (6)	0.11
Klebsiella spp.	14 (18)	13 (10)	0.12
P. aeruginosa	18 (23)	37 (29)	0.32
Polymicrobial bacteraemia	23 (30)	12 (10)	0.0002
Other GNB, *n* (%)	15 (19)	20 (16)	0.53
>1000 CFUs from CVC, *n* (%)	36 (46)	18 (14)	<0.0001
Multidrug-resistant G – bacilli, *n* (%)	3 (4)	12 (10)	0.13

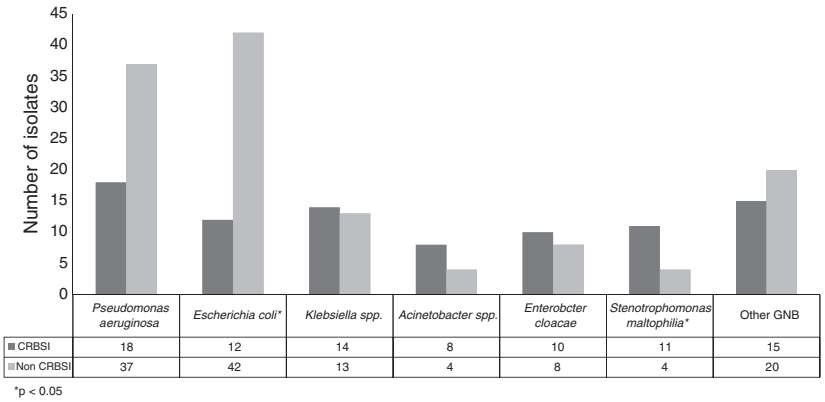

FIG. 2. Microbiology of CRBSI and non-CRBSI among hospitalized cancer patients with central venous catheter.

TABLE 2. Individual factors independently associated with gram-negative CRBSI on multiple logistic regression analysis

Effect	OR estimate	95% CI limit	
S. maltophilia bacteraemia	5.78	1.47	22.78
Polymicrobial bacteraemia	4.04	1.56	10.44
>1000 CFUs from CVC	4.39	2.02	9.57
Neutropenia	0.26	0.13	0.53

Multivariate analysis

We included all variables with a p-value for association with CRBSI of 0.25 or less (polymicrobial bacteraemia; high colony count (>1000 CFUs) by CVC; *E. coli*, *Klebsiella* spp., *Acinetobacter* spp., *E. cloacae*, *S. maltophilia* and multidrug-resistant GNB; cancer type; neutropenia; graft-versus-host-disease; prior antibiotic use; chills; duration of catheterization ≥50 days; and local tenderness at the CVC insertion site) in a logistic regression model. In this multivariate analysis, the factors independently associated with CRBSI were *S. maltophilia* bacteraemia (odds ratio (OR), 5.78; 95% confidence interval (CI), 1.47–22.78), polymicrobial bacteraemia (OR, 4.04; 95% CI, 1.56–10.44), more than 1000 CFUs on CVC blood culture (OR, 4.39; 95% CI, 2.02–9.57), and neutropenia (OR, 0.26; 95% CI, 0.13–0.53) (Table 2). When we used a predictive probability of more than 0.6 as an arbitrary cut-off for diagnosis of CRBSI our model had a sensitivity of 50%, specificity of 95%, false-positive rate of 14.6% and false-negative rate of 23.5%.

Discussion

Our data show significant differences in the microbiological and clinical characteristics of CRBSI vs. non-catheter-related GNB. *S. maltophilia* and polymicrobial bacteraemia, as well as high colony counts (>1000 CFU/mL) in a blood culture drawn through a CVC, characterized patients with CRBSI, while neutropenia was significantly more likely among patients with bacteraemia unrelated to catheters.

On univariate analysis, *E. coli* was a more common cause of bacteraemia, unrelated to CVC use. Martino [11] found that *enterobacteriaceae*, a group that included *E. coli*, caused more bacteraemia of unknown source and were less often catheter-related than other gram-negative bacilli among patients with haematological malignancies. Cytotoxic chemotherapy often affects the gastrointestinal tract of many cancer patients [12]. Normal gut flora, which include *E. coli* and other *enterobacteriaceae,* can subsequently gain access to the bloodstream. Conversely, *S. maltophilia* was associated with CRBSIs, and this effect was independent of any other tested variable in our logistic regression model. Boktour *et al.* [13] previously found that most *S. maltophilia* bacteraemias in cancer patients were CVC related and also noted that those cases had a better response to antibiotics than did other *S. maltophilia* infections if the CVC was also removed. Biofilm formation seems to be mediated by *S. maltophilia fimbriae* [14] and enhanced by other features such as hydrophobicity and less motility among *S. maltophilia* strains [15,16]. Biofilm formation may also be affected by physical factors [17] and antibiotic use [18].

Polymicrobial GNB was more common among CRBSI cases than among non-CRBSI cases. Biofilms have been described as being composed of multiple bacteria arranged in microcolonies [19,20]. Furthermore, polymicrobial bacteraemia is not uncommon in cancer patients [21]. Klastersky *et al.* [22] reported that 10% of bacteraemias among cancer patients with febrile neutropenia involved two or more bacteria types. This association is worrisome because polymicrobial bacteraemias have a higher mortality rate than do those with a single isolate [23]. In cancer patients, Elting *et al.* [24] found that polymicrobial BSI also had a lower response rate to antibiotics. In CRBSIs, the source of the infection can be removed, which has been found to help prevent relapses in gram-negative CRBSI [9]. Further investigation is needed regarding the epidemiological characteristics of polymicrobial bloodstream infections in cancer patients and the mechanisms required to prevent colonization of indwelling devices by multiple organisms.

Neutropenia is a known risk factor for GNB [25–28]. However, in this current study, we found that neutropenia was independently associated with non-CRBSIs. Our results are consistent with those of Boktour *et al.* [13], who found that neutropenic patients with *S. maltophilia* bacteraemia were less likely to have a CRBSI. In another study at our institution, Raad *et al.* [4] reported that the proportion of GNBs classified as CRBSIs among the predominantly neutropenic patients with haematologic malignancy was significantly lower than that among solid tumour patients [4]. This effect was not seen among patients with gram-positive infections. On further analysis, most of the difference could be explained by a high frequency of neutropenia among patients with haematological malignancies compared with patients with solid tumours. Therefore, patients with neutropenia in our study may have been at higher risk of bacteraemia from a different, non-catheter, source such as their gastrointestinal or genitourinary tract.

A quantitative blood culture from the CVC of >1000 CFUs was strongly associated with CRBSI. Capdevila *et al.* [29] proposed that a high colony count (>100 CFUs) on blood culture drawn from the CVC, along with peripheral

blood culture positive for the same organism, was an accurate diagnostic tool for CRBSI. Similarly, Safdar *et al.* [30] conducted a meta-analysis and estimated a pooled sensitivity of 84% and specificity of 90% for a high colony count (>100 CFU/mL) in a quantitative blood culture drawn through the CVC in establishing the diagnosis of CRBSI. Although a high colony count from a CVC blood culture by itself is not diagnostic of CRBSI, it is reasonable to use this test for screening purposes with a low threshold for CVC removal or exchange in cancer patients with GNB.

There were certain limitations to our study. We were unable to ascertain retrospectively where the infection was acquired. This was a retrospective study. Factors negatively associated with CRBSIs are not necessarily protective against CRBSIs but rather are more common in other types of infection. We did not record information regarding the presence of abdominal symptoms such as diarrhoea and abdominal pain that may indicate the possibility of colitis or the source of gram-negative bacteraemia. In addition, this was a single-centre study focused on cancer patients. The results may not be translated to a general population.

Several factors may assist clinicians in making a decision as to when a CVC is the source of a GNB and hence CVC removal may be considered. Our analysis of 204 gram-negative BSI cases revealed intriguing differences in the microbiological and clinical characteristics of CRBSIs vs. non-CRBSIs. *S. maltophilia* is a common cause of gram-negative CRBSI; polymicrobial infections are also strongly suggestive of a CRBSI. A high colony count obtained from a quantitative blood culture drawn through a CVC is a strong predictor of CRBSI. Hence, a low threshold for CVC removal maybe warranted in all of these situations. Neutropenic patients are probably at a higher risk of bacteraemia from sources besides the CVC.

Acknowlegements

None.

Transparency Declaration

Conflicts of interest: nothing to declare. Financial disclosures: none.

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